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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FREDMAN, JEFFREY NORMAN	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 10/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/836,734	BECKMANN ET AL.	
	Examin r	Art Unit	
	Jeffrey Fredman	1634	

-- Th MAILING DATE of this communication app ars on th cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8,15-18 and 20* is/are pending in the application.

4a) Of the above claim(s) *5 and 7* is/are withdrawn from consideration.

5)☒ Claim(s) *1-4,15 and 17* is/are allowed.

6)☒ Claim(s) *8,16,18 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status

1. This action is non-final since new rejections, not necessitated by Applicant's amendment, are presented. Any rejection which is not reiterated in this action is hereby withdrawn as no longer applicable.

Election/Restrictions

2. The Restriction requirement made in the office action mailed February 27, 1998 is still in effect. In the previous office action, the protein claims were inadvertently examined. However, the claims remain distinct and burdensome for the reasons of record in the original restriction requirement. To further evidence the burden, a word search of Medline and Biosis on October 15, 2003, found 964 references which use the word calpain within 9 words of isolate, purify, characterize or identify. Of these, 399 are in 1994 or earlier (356 in 1993 or earlier). There would be significant separate burden to obtain and review the references which would relate to the protein. Therefore, the restriction requirement is maintained. Applicant was requested to elect a Group. During a telephone conversation with Gary Tanigawa on October 14, 2003, Applicant affirmed the election to the nucleic acid group which had already been examined. Therefore, claims 5 and 7 are withdrawn from further prosecution as drawn to a non-elected invention.

Claim interpretation

3. The term "complementary" in claim 2 is interpreted to mean "fully complementary" since this is the normal definition of this term and since the specification does not offer any other definition of the term "complementary".

Allowable Subject Matter

4. Claims 1-4, 15 and 17 are allowed.

5. The following is a statement of reasons for the indication of allowable subject matter: Claims 1-4, 15 and 17 are drawn to novel nucleic acid sequences and to methods of detecting the presence or absence of these sequences. The prior art does not teach or suggest the specific sequences claimed.

Claim Rejections - 35 USC § 112 – Written Description

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 16 and 18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number'' depends on whether one of skill in the art would recognize that the applicant was in

possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

Claims 16 and 18 encompass a genus of nucleic acids which are different from those disclosed in the specification. In this case, the genus is any primer that is "obtained from the primers defined in a)." Since the word "obtained" simply implies that the primer of a) is the starting material, with any changes permitted, this claim lacks any common element or functional attribute other than detection of a predisposition to LGMD2. This large genus is represented in the specification by only the particularly named SEQ ID Nos 62 and 63. Thus, applicant has express possession of only two primers in a genus which comprises hundreds of millions of different possibilities. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations is provided.

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that

> "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection

> because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. "

In the current situation, the definition of the "primers obtained from SEQ ID NO: 62 and 63" lack any specific structure. This is precisely the situation of naming a type of material which is generally known to likely exist, but, except for the two specific primers, is in the absence of knowledge of the material composition and fails to provide descriptive support for the generic claim to any primer obtained from these sequences.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

The current situation is a definition of the compound solely but its functional utility, as a primer, without any definition of the particular primers claimed.

In the instant application, certain specific SEQ ID NOs are described. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of any nucleic acids other than those expressly

disclosed which comprise "primers obtained from the primers defined in a)". Therefore, the claims fail to meet the written description requirement by encompassing sequences which are not described in the specification.

Claim Rejections - 35 USC § 112 - Enablement

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 8 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids and in vitro host cells, does not reasonably provide enablement for pharmaceutical compositions of nucleic acids for gene therapy or for in vivo host cell expression of LGMD2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to pharmaceutical compositions for treatment of LGMD2 disease which comprise isolated nucleic acids and host cells, which includes cells in vivo, that are used for gene therapy methods and in vivo protein expression methods for treatment. The invention is in an class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims encompass compositions which use or result from gene therapy in humans whose recited outcome is to treat LGMD2 disease. No specific chemical compounds which function to increase the expression of LGMD2 have been identified in the specification. No specific type of LGMD2 disease is recited and thus the claims encompass any variant of the disease, whether involving overexpression of LGMD2, underexpression of LGMD2 as well as downstream effects of LGMD2 in which an altered protein may otherwise cause disease but be expressed at normal levels. No specific cell types are recited so the term "disease cells" encompasses a extensive and diverse number of different cell types.

Quantity of Experimenation

The quantity of experimentation in this area is extremely large since determination of the efficacy of these prostate specific transglutaminase, cytokeratin 15 or semenogelin II expression systems would require, initially, in vitro studies to demonstrate proof of principle. That is, prior to any therapeutic intervention, it would be

necessary to create a viral expression vector or plasmid which could be expressed therapeutically, show that expression of prostate specific transglutaminase, cytokeratin 15 or semenogelin II occurs in sufficient quantity and number of cells to have effect, then show that this effect would have some therapeutic effect on cells, a series of showings not present in the specification. Following such experimentation, animal models would need to be characterized, an inventive, unpredictable and difficult undertaking in itself, and efficacy would need to be demonstrated in such animal models. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The unpredictability of the art and the state of the prior art

The art teaches that gene therapy is, if not the most, one of the most unpredictable areas of human endeavor for which patents are sought.

Thomas et al, in 2003 (Nature Rev. Gen. 4:346-358) states regarding gene therapy that "enthusiasm rapidly waned as clinical trial after clinical trial failed to show efficacy (see page 346, column 1)". Thomas further notes that the first gene therapy success EVER occurred in 2000, but that the therapy was not reliable since it caused leukemia in 2 of the 11 treated patients (see page 346, column 1).

The prior art teaches that methods of gene delivery to cells are currently unpredictable when using either viral mediated delivery approaches, naked DNA or facilitated DNA delivery approaches. Orkin (in Recommendations to the NIH) teaches that as yet these obstacles have not been overcome in the attempt to provide workable methods of gene therapy. Among problems cited with viral hosts are their low titers, poor expression, and mutagenic capabilities. Viral vectors such as adenovirus are

taught as being immunogenic in their own right. Naked DNA and facilitated DNA approaches both have problems in poor stability of DNA, (DNA is frequently taken up by endosomes of the cell) and unpredictable copy number and/ or expression. In all cases low and transient expression of introduced genes is a significant problem. Further Mulligan teaches that in the specific case of tumor infiltrating lymphocytes used to express foreign genes "neither the capacity of TIL to traffic to tumor in vivo nor the mechanism of antitumor activity of TIL has been adequately established" (see page 930, column 2).

Further, with regard to the nucleic acid molecule expression treatment claims, the bulk of the art indicates the difficulty regarding gene delivery in vivo, for example, Harris et al (Trends Genetics (1996) 12(10):400-405) states regarding gene therapy that "The major hurdle now is the poor efficiency of gene delivery in vivo with the gene transfer technology presently available, but we anticipate that this will be overcome by further modifications of viral vectors and the development of synthetic systems combining the best elements of a variety of vectors. (Page 405)".

The prior art also supports the unpredictable nature of the art. It is unpredictable which formulations, compounds and delivery modes will function in an in vivo setting. This unpredictability is evidenced by a report in Science (269:1050-1055) which states that "So far, there has been no unambiguous evidence that genetic treatment has produced therapeutic benefit (page 1050, column 1)". Thus, the prior art not only fails to support the efficacy of the invention, but in fact, supports the unpredictability of this area of technology.

Working Examples

The specification has no working examples, whatsoever, of treatments which effect the expression of LGMD2 by gene therapy.

Guidance in the Specification.

The specification, while mentioning gene therapy, provides absolutely no guidance whatsoever on modes and means of performing gene therapy. No specific teachings regarding the use of the particular LGMD2 constructs with any success is presented. No teachings are provided that the LGMD2 constructs claimed are able to express satisfactory levels of protein over a sufficiently long term to be efficient as a therapeutic agent and no teachings are provided as to the amounts of cells that would have to be provided or the lengths of time over which such cells would have to be provided to effectively treat LGMD2. It would essentially be a trial and error process to make and use the LGMD2 molecules encompassed by the claims, and to express these at a satisfactorily high level for a sufficient period of time within a human being or other animal model. It is further not predictable that these altered cells would be effective to achieve any therapeutic benefit in LGMD2 cells.

Level of Skill in the Art

The level of skill in the art is deemed to be high with regard to the practitioners but low relative to the ability to perform gene therapy, since as of the filing date of this application, gene therapy had never been successful in treating a disease in humans (see Thomas, page 346, column 1, where the first, and so far only success, occurred in the year 2000).

Conclusion

In the instant case, as discussed above, the level of unpredictability in the art is high (see Thomas, Marshall in science, Harris et al.and Orkin) , the specification

provides one with no written description or guidance that leads one to a reliable method of treatment. One of skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains . Further the specification does not provide guidance to overcome art recognized problems in gene therapy required to actually use the LGMD2 sequences recited in a treatment as broadly claimed (i.e encompassing a therapeutic composition in human beings). Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of any working examples and the negative teachings in the prior art balanced only against the high skill level in the art, it is an inescapable conclusion that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

10. Applicant's arguments filed August 5, 2003 have been fully considered but they are not persuasive.

The only arguments which remain relevant are drawn to the enablement rejection. Applicant argues that not all of the Wands factors were addressed. While with regard to the previous action that may be true, in the current action, all of the factors are addressed.

Applicant then argues that as of the Orkin report, in 1995, 106 clinical trials were underway, which purports to prove a high level of skill in the art. While the artisan may be highly skilled, the art clearly lacked the skill to perform gene therapy. As Thomas notes in 2003, the first gene therapy success in any clinical trial did not occur until 2000.

So in 1995, when this application was already pending a year, no gene therapy trial was successful which would evidence a low state of the art (see page 346, column 1). Consequently, the large number of clinical trials which ALL FAILED supports a finding of that the claims are not enabled.

The citation of references such as Quantin and Stratford, who do not show any therapeutic effect, has no impact on the enablement analysis. These references simply show relevant information. However, they fail to enable gene therapy in an application which lacks any support where the totality of the prior art notes that Gene therapy has never succeeded.

The evidence of Annex III is too little, too late. The evidence is too little since it does not show gene therapy in patients, but simply proves that the protein can transiently be expressed in certain cell types. The evidence is also too little since it is not in the form of a Declaration. This is not evidence that Gene therapy in patients would works. The evidence is too late and not commensurate in scope with the claim since there is no teaching in the specification of the specific vector, of the specific methods or of any specifics associated with the invention.

For these reasons, the rejections are maintained.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1634